The basis of the present invention is the construction of a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia over a time course of administration without loss of analgesic potency. Within general definitions accepted by medical practitioners and research scientists, each and every representative example of this general class of chimeric hybrid conjugate molecules is deemed capable of delivering analgesia without the development of opioid tolerance and as such, possesses intrinsic anti-tolerance properties that are functionally determined by its chemical structure. Furthermore, the general class of chimeric hybrid conjugate molecules, designed to contain an opioid analgesic moiety or principle capable of engendering opioid-dependent analgesia without opioid tolerance development, possesses well established, clinically-efficacious, pharmacological properties for acute and chronic pain relief that are operationally defined by those of the prototype opioid alkaloid morphine. As such, a general class of chimeric hybrid conjugate molecules capable of engendering efficacious, morphine-like, opioid-dependent analgesia for a variety of clinically defined pain indications without tolerance development is novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

he novelty of the present invention is not predictable according to the teachings of Rothman (1) who has formulated models and mechanisms of morphine and opioid tolerance and dependence that are exclusively mediated by functional changes in receptors and peptide transmitter systems within the CNS. Notably, Rothman teaches that adaptive mechanisms of morphine tolerance and dependence involve CNS neuropeptide systems that normally mediate homeostatic responses to attenuate adverse physiological effects of prolonged morphine exposure. The present invention is a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without opioid tolerance development that is functionally dependent on simultaneous activation of mu opioid and substance P receptors within the CNS following parenteral administration outside the CNS morphine and, as such, its pharmacological effects are intrinsically a function of this class of molecules to permeate the mammalian blood brain barrier (BBB) as an intact chemical entity. Accordingly, the analgesic and anti-opioid tolerance properties of this general class of chimeric hybrid conjugate molecules are functionally linked to chemical and pharmacological integrity of each of the receptor activating domains to effectively permeate the BBB within a capped covalently bonded linear sequence. According to the teachings of Rothman, it is not intuitively obvious and predictable that molecules of the general class of chimeric hybrid conjugate molecules possessing an opioid analgesic moiety or principle capable of engendering clinically-efficacious, opioid-dependent, acute and chronic pain relief equivalent to that produced by the prototype opioid alkaloid morphine will activate homeostatic anti-tolerance mechanisms within the CNS. As such, the requirement for an intact chimeric hybrid conjugate molecule to permeate the mammalian BBB as an intact chemical entity to enable each of its mu opioid and substance P receptor (MOR and SPR, respectively) activation domains to effect clinically efficacious opioid analgesia without tolerance development distinguishes the present invention as novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention is not predictable according to the teachings of Foran and coworkers (2) in reference to those of Rothman. Foran and coworkers teach that repeated administration of a chimeric peptide containing MOR and SPR activation domains into the rat CNS produces opioid-dependent analgesia without tolerance development that is functionally linked to its SPR activation domain. Because the present invention is a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without opioid tolerance development that is functionally dependent on simultaneous activation of MORs and SPRs within the CNS following parenteral administration outside the CNS, its pharmacological effects are intrinsically a function of this class of molecules to permeate the mammalian BBB as an intact chemical entity. As such, the requirement for an intact chimeric hybrid conjugate molecule to permeate the mammalian BBB as an intact chemical entity to enable each of its MOR and SPR activation domains to effect clinically efficacious opioid analgesia without tolerance development is not predictable by the teachings of Foran and coworkers in reference to those of Rothman and distinguishes the present invention as novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention is not predictable according to the teachings of Nyberg and coworkers (3), in reference to the teachings of Foran and coworkers and Rothman. Nyberg and coworkers teach that CNS metabolism of SP and SPR activation domains via SP-specific endopeptidase activity is altered following morphine tolerance development and significant increases in SP-specific endopeptidase activity may be responsible for compensatory physiological responses in opioid tolerant animals. Because the present invention is a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without opioid tolerance development that is functionally dependent on simultaneous activation of MORs and SPRs within the CNS following parenteral administration outside the CNS, its pharmacological effects are intrinsically a function of this class of molecules to permeate the mammalian BBB as an intact chemical entity. As such, the requirement for an intact chimeric hybrid conjugate molecule to permeate the mammalian BBB as an intact chemical entity to enable each of its MOR and SPR activation domains to effect clinically efficacious opioid analgesia without tolerance development without altering compensatory SP-metabolizing systems is not predictable by the teachings of Nyberg and coworkers in reference to those of Foran and coworkers and Rothman and distinguishes the present invention as novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention as a general class of chimeric hybrid conjugate molecules capable of engendering efficacious opioid-dependent analgesia without tolerance development that is functionally dependent on BBB transport is not predictable according to the teachings of Syvanen and coworkers (4) who studied influx and efflux processes of morphine and morphine-glucuronides in relation to their BBB permeability properties and brain concentrations. Syvanen and coworkers teach that efficacious BBB permeation is determined by a combination of influx hindrance (a

gatekeeper function in the luminal membrane that is functionally linked to P-glycoprotein activation) and efflux enhancement by transporters that pick up molecules on one side of the luminal or abluminal membrane and release them on the other side. The production of opioid-dependent analgesia for acute and chronic pain indications via a facilitative method of BBB transport of morphine and morphine congeners by covalently bonded heterologous SPR, or for that matter representative members of other classes of neuropeptide receptor, activation domains as found in the structure of chimeric hybrid conjugate molecules is not predictable by the general principle of BBB permeation by morphine and morphine congeners codified by Syvanen and coworkers. Conversely, the production of opioid-dependent analgesia for acute and chronic pain indications via the facilitative method of BBB transport of SP fragments or non-peptide SPR, or for that matter representative peptide or non-peptide members of other classes of neuropeptide receptor, activation domains by covalently bonded heterologous morphine, morphine congeners, and opioid peptide MOR activation domains as found in the structure of chimeric hybrid conjugate molecules is not predictable by the teachings of Syvanen and coworkers.

In light of the work of Syvanen and coworkers cited above, the teachings of Liederer and coworkers (5) provide us with guidelines by which to construct a general class of chimeric hybrid conjugate molecules capable of opioid-dependent analgesia for acute and chronic pain indications that combine any non-peptide opioid with any active fragment of SP, or for that matter any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain, for transport across the BBB. Liederer and coworkers teach that low BBB permeation is functionally linked to strong substrate activity for P-glycoprotein and efflux transporters in this biological barrier that is markedly enhanced for a variety of tested opioid peptide analogs sharing a common covalent cyclical structure. In contrast, capped, electrically neutral, linear derivatives of a variety of opioid peptide analogs with acetylation of the N-terminal and amidation of the C-terminal ends display efficacious permeation of the BBB via low substrate activity for P-glycoprotein and efflux transporters in this biological barrier.

Application of guidelines derived from the teachings of Liederer and coworkers in reference to the teachings of Syvanen and coworkers will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1, i.e., a general class of chimeric hybrid conjugate molecules capable of producing opioid-dependent analgesia for acute and chronic pain indications without tolerance development via simultaneous activation of MORs and SPRs, or for that matter any other class of neuropeptide receptors, within the CNS. Chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of SP, or for that matter any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain, for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB are constructed as capped, electrically neutral, linear sequences with the non-peptide opioid covalently bonded to the N-terminal end of the SP fragment, or for that matter any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain, through a 4-6 carbon molecular linker and containing a neutral amide group at

the C-terminal end of the SP fragment or any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain. Chimeric hybrid conjugate molecules that combine any opioid peptide, or for that matter any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, with any non-peptide SPR activation domain for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB are constructed as capped, electrically neutral, linear sequences with acetylation of the N-terminal of the opioid peptide, or for that matter any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, that is covalently bonded at the C-terminal end to the non-peptide SPR activation domain through a 4-6 carbon molecular linker. Finally, the teachings of Schiller (6) in reference to those of Syvanen and coworkers (4) and Liederer and coworkers (5) demonstrate a permissive chemical heterocyclic substitution in the internal domains of capped linear opioid peptide sequences that allow for efficacious BBB permeation, thereby providing validation for our specification indicating d-glucuronic acid, as a representative example of a closed-ring carbon structure, as an appropriate 6 carbon linker connecting linear MOR and SPR, or for that matter any other class of neuropeptide receptor, activation domains within chimeric hybrid conjugate molecules.

The production of opioid-dependent analgesia for acute and chronic pain indications via a facilitative method of BBB transport of morphine and morphine congeners by covalently bonded heterologous SPR, or for that matter any other class of neuropeptide receptor, activation domains or conversely, of BBB transport of SP fragments or non-peptide SPR activation domains, or for that matter any active fragment or non-peptide congener of any peptide possessing a pharmacologically distinct C-terminal activation domain, by covalently bonded heterologous morphine, morphine congeners, and opioid peptide MOR activation domains, requires maintenance of opioid and SP activities, or for that matter any active fragments of any peptides possessing distinct pharmacological activities, in chemically-modified structures of chimeric hybrid conjugate molecules. The teachings of Portoghese and coworkers (7, 8) in reference to those of Liederer and coworkers and Schiller provide specific indications for maintaining opioid activity following chemical modification of the multi-ringed non-peptide structures characteristic of morphinans, benzomorphans, and phenylpiperidines, as described for opioid peptide analogs. The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claim 1, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other class of neuropeptide receptors, within the CNS to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

In brief, the teachings of Portoghese and coworkers provide the following guidelines for preserving high affinity MOR activity for all non-peptide opioid domains

found in the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other neuropeptide receptors, within the CNS. Their teachings indicate that the A ring OH group at position 3 must be conserved during synthesis and/or conjugation to active SP fragments, or for that matter any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain, though a linker molecule. Consistent with the major body of published opioid research, conservation of the A ring OH group at position 3 is required for high affinity MOR activation. Thus, the A ring OH group at position 3 may be protected during synthesis or conjugation via covalent linkage to well recognized blocking groups that include Acetyl or T-butyl moieties. Following synthesis or construction of chimeric hybrid conjugates the Acetyl or T-butyl moieties are removed by gentle chemical treatment yielding non-peptide chemical moieties with a free A ring OH group at position 3.

The teachings of Portoghese and coworkers also indicate that the B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure is an appropriate site for chemical modification due to its location at a point distal to the obligate A ring OH group at position 3 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure. Chemical modification and linkage of the non-peptide opioid domain of molecules of the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other classes of neuropeptide receptors, within the CNS at a position spatially separated and distal to the obligate A ring OH group will permit binding in a sterically unhindered fashion to the mu opioid receptor. The B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure may be further oxidized to a keto group with full retention of opioid activity. OH and keto groups are generally employed as chemical moieties capable of covalently linking discrete chemical entities through ester or ether chemistry. Finally, the teachings of Portoghese and coworkers indicate that multiple positions of the B ring, including the OH group at position 6 of morphine, or an equivalent position on the morphinan or benzomorphan multi-ringed structure, may be chemically modified without effecting opioid activity mediated by the obligate A ring OH group.

The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences, or for that matter any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller, an authority in the design and synthesis of chemically modified opioid peptide sequences, and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claim 1, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other class of neuropeptide receptors, within the CNS to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

Guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller, an authority in the design and synthesis of chemically modified opioid peptide sequences, are extended to cover the breadth of all active fragments of any peptide possessing a pharmacologically distinct N-terminal activation domain by the teachings of Shimizu and coworkers (9) and by the teachings of Jette and coworkers (10). Shimizu and coworkers teach that the intact N-terminal 14 amino acid fragment of the complete 34 amino acid sequence of parathyroid hormone (PTH) represents the pharmacologically distinct N-terminal activation domain for the PTH receptor (9). Limited substitution within the autonomous pharmacologically distinct N-terminal activation domain of PTH, designated PTH (1-14), by the un-natural amino acid alpha-aminoisobutyric acid dramatically enhances the capacity of PTH (1-14) to activate the PTH receptor by 2-4 orders of magnitude (9). In similar fashion, the teachings of Jette and coworkers indicate that the N-terminal 29 amino acid peptide fragment of the complete 44 amino acid peptide sequence of human Growth Hormone-releasing factor (hGRF) represents the pharmacologically distinct N-terminal activation domain for the hGRF receptor (10). The teachings of Jette and coworkers also provide enablement for increasing the biological activity of the N-terminal 29 amino acid peptide fragment of hGRF, designated hGRF(1-29), via the method of conjugation of hGRF(1-29) through amino acid 29 to an appropriate carrier protein protein (10).

The teachings of Shimizu and coworkers (9) and Jette and coworkers (10) indicate chemical modifications and strategically defined points of chemical conjugation, i.e., positions spatially separated and distal to the N-terminal, of autonomous distinct N-terminal activation domains represented by the peptide fragments PTH (1-14) and hGRF (1-28), respectively, will dramatically enhance biological activities. Because PTH (1-14) and hGRF (1-28) themselves mediate different, physiologically distinct, pharmacological activities, as well as different, physiologically distinct, pharmacological activities as established for morphine, morphine congeners, and N-terminal activation domains of opioid peptide fragments, guidelines provided by Portoghese and coworkers, in reference to the teachings of Liederer and coworkers and Schiller, are generalized and extended by the teachings of Shimizu and coworkers and Jette and coworkers to include the breadth of any active N-terminal fragment or non-peptide congener of any peptide possessing a pharmacologically distinct N-terminal activation domain.

These combined guidelines will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1, i.e., a general class of chimeric hybrid conjugate molecules that combine any opioid peptide, or for that matter any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, with any non-peptide SPR activation domain for transport across the BBB that are constructed as capped, electrically neutral, linear sequences, in order to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

The teachings of Cascieri and Liang (11) and Mantyh and coworkers (12) provide

specific indications for maintaining SP activity for C-terminal fragments of SP within a general class of chimeric hybrid conjugate molecules capable of producing opioid-dependent analgesia for acute and chronic pain indications without tolerance development via simultaneous activation of MORs and SPRs, or for that matter any other classes of neuropeptide receptors, within the CNS. The rules provided by Cascieri and Liang and Mantyh and coworkers are considered to be general rules for evaluating bioactivities of fragments of SP by established investigators in SP research. According to their teachings and consistent with generally accepted formulations, all fragments of SP maintaining a fully intact C-terminal peptide domain equal to or greater than 5 amino acids have been determined to possess biological activity using a variety of testing paradigms. In the present invention, biologically active fragments of SP include SP 3-11, SP 4-11, SP 5-11, SP 6-11, and SP 7-11. All biologically active SP fragments contain only one free alpha amino group that is located at a site distal to SPR recognition domain and is utilized as the point of linkage of all active fragments of SP within the structure of the class of chimeric hybrid molecules described in the present invention.

Guidelines and rules provided by Cascieri and Liang (11) and Mantyh and coworkers (12), established authorities in the synthesis and structure-function relationships of SPR activation domains, for maintaining SP activity within the class of C-terminal fragments of SP, are extended to cover the breadth of all active fragments of any class of peptides possessing a pharmacologically distinct C-terminal activation domain by the teachings of Wulff and coworkers (13) and by the teachings of Smith and coworkers (14). Wulff and coworkers teach that the intact amidated C-terminal 17 amino acid fragment of the complete 28 amino acid sequence of vasoactive intestinal polypeptide (VIP), designated VIP (12-28), represents the pharmacologically distinct C-terminal activation domain for the VIP receptor (13). The teachings of Smith and coworkers indicate that the intact amidated C-terminal 11 amino acid peptide fragment of Human gastrin-releasing peptide (hGRP) represents the pharmacologically distinct autonomous C-terminal activation domain for the hGRP receptor (14). The teachings of Smith and coworkers also provide enablement for increasing the biological activity of the C-terminal 11 amino acid peptide fragment of hGRP via selected chemical modification and conjugation of the fragment through its N-terminus to a chemical stabilizer group (14).

Consistent with guidelines and rules provided by Cascieri and Liang and Mantyh and coworkers for maintaining SPR activation by C-terminal fragments of SP, Wulff and coworkers and Smith and coworkers teach that all biologically active fragments of VIP and hGRP contain only one free alpha amino group that is located at a site distal to the VIP and hGRP receptor recognition domains and may be utilized as the point of covalent linkage within the structure of the class of chimeric hybrid molecules described in the present invention. Because VIP and hGRP themselves mediate different, physiologically distinct, pharmacological activities, as well as different, physiologically distinct, pharmacological activities as established for SP and biologically active C-terminal fragments of SP, guidelines provided by Cascieri and Liang and Mantyh and coworkers, are generalized and extended by the teachings of Wulff and coworkers and Smith and coworkers to include the breadth of any active C-terminal fragment or non-peptide

congener of any peptide possessing a pharmacologically distinct C-terminal activation domain. These combined guidelines will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claim 1, i.e., a general class of chimeric hybrid conjugate molecules that combine any pharmacologically active C-terminal fragment of SP, or for that matter any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain, with any non-peptide opioid alkaloid MOR activation domain for transport across the BBB that are constructed as capped, electrically neutral, linear sequences, , in order to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

In sum, the teachings of Cascieri and Liang and Mantyh and coworkers, extended to cover the breadth of all active fragments of any peptide possessing a pharmacologically distinct C-terminal activation domain by the teachings of Wulff and coworkers and by the teachings of Smith and coworkers, in reference to the teachings of Portoghese and coworkers, Liederer and coworkers, Schiller, Shimizu and coworkers, and Jette and coworkers, provide guidelines that will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other classes of neuropeptide receptors, within the CNS to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development.

A. Chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of SP, or for that matter any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain, to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB are constructed as capped, electrically neutral, linear sequences with the non-peptide opioid covalently bonded to the N-terminal end of the SP or any other peptide fragment through a 4-6 carbon molecular linker, or according to the teachings of Schiller a more complex heterocyclic structure, and containing a neutral amide group at the C-terminal end of the SP, or any other peptide fragment. Figure 1 depicts the construct of a linear chemical structure within the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other class of neuropeptide receptors, within the CNS that contains a representative member of the morphinan, benzomorphan, or phenylpiperidine classes of non-peptide opioid alkaloid in covalent linkage to a representative member of the class of 4-6 carbon or more complex heterocyclic molecular linker in covalent linkage to a representative member of the class of biologically active fragments of SP that include SP 3-11, SP 4-11, SP 5-11, SP 6-11, and SP 7-11, and their chemically modified congeners, as well as examples of other biologically active C-terminal peptide fragments indicated by the teachings of Wulff and coworkers (13) and by the teachings of Smith and coworkers (14)

Figure 1: Construct of a chimeric hybrid conjugate molecule that combines any non-peptide opioid with any active fragment of SP or any active fragment of any peptide

possessing a pharmacologically distinct C-terminal activation domain

Non-peptide opioid alkaloid	Molecular linker	Active fragment of SP, VIP, hGRP, or any other class of neuropeptide

Representative candidate molecules chosen from the morphinan, benzomorphan, or phenylpiperidine classes of non-peptide opioid alkaloids, 4-6 carbon or more complex heterocyclic molecular linkers, and biologically active fragments of SP, VIP, and hGRP are listed in Table 1 and one of each may be covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules according to guidelines gleaned from the teachings of Portoghese and coworkers (7, 8), Cascieri and Liang (11), Mantyh and coworkers (12), Wulff and coworkers (13), and Smith and coworkers (14), in reference to those of Liederer and coworkers (5) and Schiller (6).

Table 1: Representative molecules covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of SP, VIP, or hGRP, to produce opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB.

Non-peptide opioid alkaloids	Molecular linkers	Active fragments of substance P
Morphine	Succinic acid	substance P 3-11
Dihydromorphine	Gamma hydroxybutyric acid	substance P 4-11
Oxymorphone	d-glucuronic acid	substance P 5-11
Oxycodone	l-glucuronic acid	substance P 6-11
Hydrocodone	oxaloacetic acid	substance P 7-11
Pentazocine	alpha ketoglutaric acid	D-nor-leu substance P 3-11
Cyclazocine	inositol	D-nor-leu substance P 4-11
Fentanyl	tetrahydroisoquinoline-3-carboxylic acid	D-nor-leu, D-tryp substance P 3-11
Sufentanyl		D-nor-leu, D-tryp substance P 4-11
		VIP (12-28)
		hGRP 11 amino acid C-terminal fragment

B. Chimeric hybrid conjugate molecules that combine any MOR-preferring opioid peptide, or for that matter any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, with any non-peptide SPR receptor activation domain for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB are constructed as capped, electrically neutral, linear sequences with acetylation or equivalent chemical modification of the N-terminal of the opioid peptide, or any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, that is covalently bonded at the C-terminal end to the non-peptide SPR activation

domain through a 4-6 carbon molecular linker, or according to the teachings of Schiller (6) a more complex heterocyclic structure. Figure 2 depicts the construct of a linear chemical structure within the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other class of neuropeptide receptors, within the CNS that contains a representative member of the class of MOR-preferring opioid peptide, *or any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain*, in covalent linkage to a representative member of the class of 4-6 carbon or more complex heterocyclic molecular linker in covalent linkage to a representative member of the class of non-peptide SPR activation domain.

Figure 2: Construct of a chimeric hybrid conjugate molecule that combines any MOR-preferring opioid peptide, or any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain with any non-peptide SPR activation domain.

MOR-preferring opioid peptide fragment PTH (1-14), hGRF (1-28), or any other pharmacologically distinct N-terminal activation domain	Molecular linker	Non-peptide SPR activation domain

Representative candidate molecules chosen from the class of MOR-preferring opioid peptides, or any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, 4-6 carbon or more complex heterocyclic molecular linkers, and non-peptide SPR activation molecules are listed in Table 2 and one of each may be covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules according to guidelines gleaned from the teachings of Portoghese and coworkers (7, 8), Shimizu and coworkers (9), Jette and coworkers (10) Cascieri and Liang (11) and Mantyh and coworkers (12) in reference to those of Liederer and coworkers (5) and Schiller (6).

Table 2: Representative molecules covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules that combine any MOR-preferring opioid peptide, or any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain with any non-peptide SPR activation domain for production of opioid-dependent analgesia for acute and chronic pain indications without tolerance development via transport across the BBB.

MOR-preferring opioid peptides or any active fragment of any peptide possessing a pharmacologically distinct	Molecular linkers	Non-peptide substance P receptor activating molecules

N-terminal activation domain		
N-acetyl methionine enkephalin N-acetyl methionine enkephalin-Arg-Phe N-acetyl, D-ala2, methionine enkephalin N-acetyl leucine enkephalin N-acetyl leucine enkephalin-Arg-Gly-Leu N-acetyl,D-ala2, leucine enkephalin N-acetyl dynorphin A (1-13) N-acetyl endomorphin 2 PTH (1-14), hGRF (1-28), or any other pharmacologically distinct N-terminal activation domain	Succinic acid Gamma hydroxybutyric acid d-glucuronic acid l-glucuronic acid oxaloacetic acid alpha ketoglutaric acid inositol tetrahydroisoquinoline-3-carboxylic acid	L-733,061 (partial agonist) GR7362 RP67580 (partial agonist)

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Response to Paragraph 6

A. (12/13/05 Office Action Par. 6.A) Further defined in Responses to Paragraphs 4 and 5, above.

B. (12/13/05 Office Action Par. 6.B) Further defined in Responses to Paragraphs 4 and 5, above.

D. (12/13/05 Office Action Par. 6.D) Further defined in Responses to Paragraphs 4 and 5, above.

Response to Paragraph 7.A

I respectfully submit that my responses to paragraphs 4 and 5 provide sufficient rationale to overturn double patenting rejections provided by 6,881,829.

Response to Paragraph 8.B

I respectfully submit that a 102(f) rejection is inapplicable. My application does not derive from U.S. Patent 6,759,520. (See Responses to Paragraphs 4 and 5.)

Derivation requires complete conception by another and '520 is not the complete conception of my present invention.

It also requires communication of that conception to the party charged with derivation prior to any date on which it can be shown that the one charged with derivation possessed knowledge of the invention. Kilbey v. Thiele, 199 USPQ 290, 294 (Bd. Pat. Inter. 1978). "Communication of a complete conception must be sufficient to enable one of ordinary skill in the art to construct and successfully operate the invention." Hedgewick, 497 F.2d at 908, 182 USPQ at 169. See also Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1577, 42 USPQ2d 1378, 1383 (Fed. Cir. 1997). This, too, did not occur.

I attach my affidavit that the statement of the inventorship of the present application is correct in that my present application discloses subject matter invented by the applicant rather than derived from the author or patentee notwithstanding the inventorship of the '520 patent.

Respectfully yours,

Attachments
Declaration

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Certificate of Faxing

I certify that this correspondence is being filed by fax to 571-273-8300 ~~703-872-9306~~ on the date below.

Date: November 2, 2006

Richard M. Kream, Ph.D.
Applicant